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A STUDY GUIDE FOR **GLAUCOMA**

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AQUEOUS HUMOR DYNAMICS

The study of glaucoma deals primarily with the consequences of elevated intraocular pressure (IOP). A logical place to begin this study, therefore, is with the physiologic factors that control IOP, which are the dynamics of aqueous humor flow.

I. HOW AQUEOUS HUMOR DYNAMICS INFLUENCE INTRAOCULAR PRESSURE

To reduce a highly complex, and only partially understood, situation to its simplest form, IOP is a function of the rate at which aqueous humor enters the eye (inflow) and the rate at which it leaves the eye (outflow). When inflow equals outflow, a *steady state* exists, and the IOP remains constant.

Inflow is related to the rate of aqueous humor production, while outflow depends on the resistance to the flow of aqueous from the eye and the pressure in the episcleral veins. The control of IOP, therefore, is a function of: 1) production of aqueous humor; 2) resistance to aqueous humor outflow; 3) episcleral venous pressure.

The remainder of this chapter deals with these three parameters and their complex interrelationship with the IOP.

II. AN OVERVIEW OF THE ANATOMY

Aqueous humor is involved with virtually all portions of the eye, although the two main structures related to aqueous humor dynamics are the *ciliary body*, the site of aqueous production, and the *limbus*, the principal site of aqueous outflow. The step-wise construction of a schematic model, as shown in Fig. 2.1, illustrates the close relationship between these two structures and the surrounding anatomy. (The histology related to aqueous production and outflow is discussed later in this chapter, and the dimensions that are important in surgical procedures are considered in Section Three.)

1. The *limbus* is the transition zone between the cornea and the sclera. On the inner surface of the limbus is an indentation, the *scleral sulcus*, which has a sharp posterior margin, the *scleral spur*, and a sloping anterior wall that extends to the peripheral cornea (Fig. 2.1a).

2. A sieve-like structure, the *trabecular meshwork*, bridges the scleral sulcus and converts it into a tube, called *Schlemm's canal*. Where the meshwork inserts into the peripheral cornea, a ridge is created, known as *Schwalbe's line*. Schlemm's canal is connected by *intrasccleral channels* to the episcleral veins (Fig. 2.1b).

The trabecular meshwork, Schlemm's canal, and the intrasccleral channels comprise the main route of aqueous humor outflow.

3. The *ciliary body* attaches to the scleral spur and creates a potential space, the *supraciliary space*, between itself and the sclera.

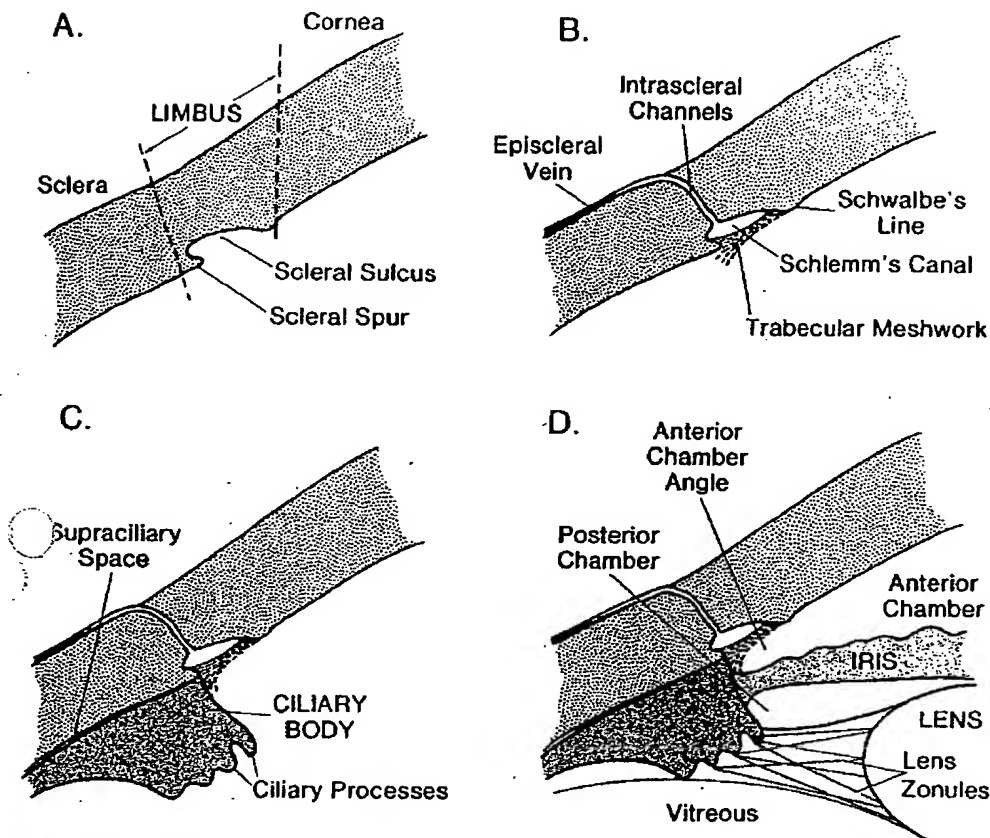


Figure 2.1. Step-wise construction of a schematic model depicts the relationship of structures involved in aqueous humor dynamics: A: Limbus; B: Main route of aqueous outflow; C: Ciliary body (site of aqueous production); D: Iris and lens.

On cross-section, the ciliary body has the shape of a right triangle, and the *ciliary processes* (the actual site of aqueous production) occupy the innermost and anteriormost portion of this structure, extending back for approximately 2 mm in the region called the *pars plicata* (or *corona ciliaris*). The posterior 4 mm of the ciliary body, the *pars plana* (or *orbicularis ciliaris*), has a flatter inner surface and joins the choroid at the *ora serrata* (Fig. 2.1c).

4. The *iris* inserts into the anterior side of the ciliary body, leaving a variable width of the latter structure visible between the root of the iris and scleral spur. The *lens* is suspended from the ciliary body by *zonules* and separates the vitreous, posteriorly, from the aqueous, anteriorly. The iris separates the aqueous compartment into a posterior and an anterior chamber, and the angle formed by the iris and the cornea is called the *anterior chamber angle* (Fig. 2.1d).

Thus, aqueous humor is produced by the ciliary processes and first

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enters the posterior chamber. It then passes forward, through the pupil, to the anterior chamber, where it leaves the eye by way of structures in the anterior chamber angle.

III. PRODUCTION OF AQUEOUS HUMOR

A. Histology of the Ciliary Body

The ciliary body is one of three portions of the uveal tract, or vascular layer of the eye. The other two structures in this system are the iris and choroid. The ciliary body measures 6 mm from the scleral spur to the ora serrata and is composed of 1) muscle, 2) vascular stroma, and 3) epithelium (Fig. 2.2):

1. The ciliary muscle consists of two main portions, the longitudinal and the circular fibers:

a. It is the *longitudinal fibers* which attach the ciliary body to the limbus at the *scleral spur*. The muscle then runs posteriorly to insert into the *suprachoroidal lamina* (fibers connecting choroid and sclera) as far back as the equator or beyond.

b. The *circular fibers* occupy the anterior and inner portion of the ciliary body and run parallel to the limbus.

c. A third portion of the ciliary muscle has been described as *radial fibers*, which connect the longitudinal and circular fibers.

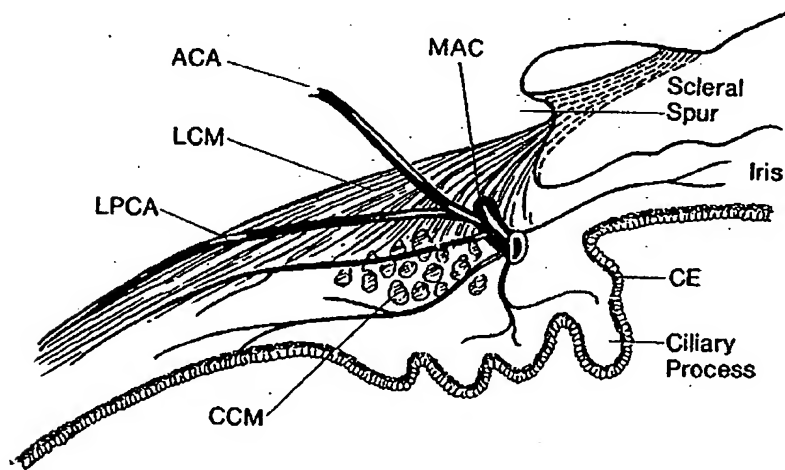


Figure 2.2. The ciliary body has three major components. (1) The ciliary muscle is primarily composed of longitudinal (LCM) and circular (CCM) fibers. (2) The vascular system is formed by branches of the anterior ciliary arteries (ACA) and long posterior ciliary arteries (LPCA). These vessels are shown forming the major arterial circle (MAC) in accordance with traditional teaching, although recent studies suggest that the major circle is supplied exclusively by the long posterior ciliary arteries.¹ (3) The ciliary epithelium (CE) is composed of an inner pigmented and an outer non-pigmented layer.

2. The vascular stroma of the ciliary body may be considered in two parts:

a. The major arterial circle lies in connective tissue stroma medial and anterior to the circular portion of the ciliary muscle. Traditional teaching holds that this vascular system is formed by anastomoses between the long posterior ciliary and the anterior ciliary arteries. However, scanning electron microscopic studies of plastic casts of human ocular microcirculation indicate that the major arterial circle is formed exclusively by paralimbal branches of the long posterior ciliary arteries.¹ The anterior ciliary arteries send branches to the iris and ciliary body, but the major arterial circle appears to be the main source of blood supply to both of these structures.

b. The ciliary processes consist of approximately 70 radial ridges composed of a capillary network and thin stroma covered by epithelium. Several precapillary arterioles from the major arterial circle supply each ciliary process. Sphincters have been noted in these arterioles just after they leave the major circle, and it has been suggested that they may influence aqueous humor production by regulating blood flow into the ciliary processes.¹ The precapillary arterioles break up into a plexus of interanastomosing capillaries within the ciliary processes and then drain predominantly into the pars plana veins.¹

3. Two layers of epithelium, an outer pigmented and an inner non-pigmented layer, line the inner surface of the ciliary processes and the pars plana.

B. Ultrastructure of the Ciliary Processes

Each ciliary process is composed of three basic components; capillaries, stroma, and epithelia (Fig. 2.3):

1. The network of capillaries occupy the center of each process and are composed of²:

a. Very thin endothelium with fenestrae, or false "pores," which represent areas of absent cytoplasm with fusion of the plasma membranes, and which may be the site of increased permeability.

b. A basement membrane surrounding the endothelium.

c. Mural cells, or pericytes, within the basement membrane.

2. A very thin stroma surrounds the capillary network and separates it from the epithelial layers. The stroma is composed of²:

a. Ground substance, consisting of mucopolysaccharides, proteins, and solute of plasma (except those of large molecular size).

b. A very few collagen connective tissue fibrils.

c. Wandering cells of connective tissue and blood origin.

3. Two layers of epithelium surround the stroma, with the apical surfaces of the two cell layers in apposition to each other (Fig. 2.4)²⁻⁵:

a. Pigmented epithelium comprises the outer layer, adjacent to stroma. These cells are low cuboidal and are characterized by numerous melanin granules in the cytoplasm and an atypical basement membrane on the stromal side.

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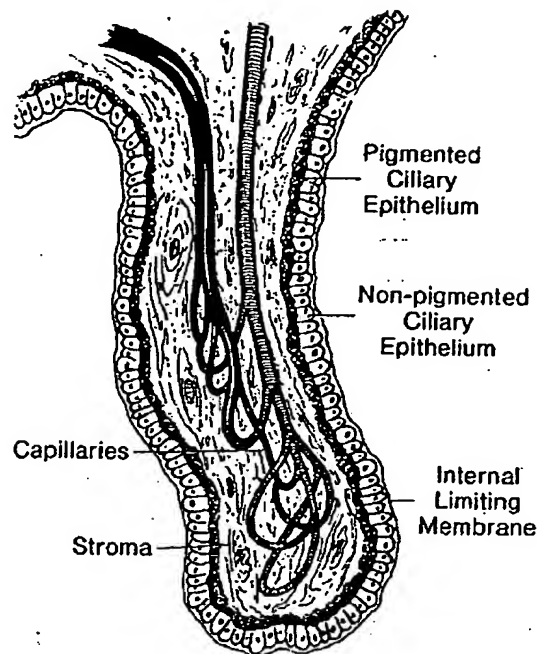


Figure 2.3. A ciliary process is composed of three elements: (1) capillaries; (2) thin stroma; and (3) two layers of epithelium.

b. *Non-pigmented epithelium* makes up the inner layer, adjacent to the aqueous in the posterior chamber. The cells of this layer are columnar and have the following characteristics.

(1). The *basement membrane* is composed of fibrils in a glycoprotein. This membrane, which faces the aqueous, is also called the *internal limiting membrane* and fuses with the lens zonules.

(2). Numerous *mitochondria* are seen in the *cytoplasm*, along with poorly developed rough and smooth endoplasmic reticulum, and a scant amount of ribosomes. Rows of vesicles near the free surface, called "pinocytic vesicles," are seen only with osmium tetroxide fixation and are felt to represent artifactual tubules cut on end.³

(3). The *nucleus* has a nucleolus that appears to contain ribosomes.

(4). The *cell membrane* is 200 Å thick and is characterized by *infoldings* or *interdigitations*, especially surface infoldings on the free surface and lateral interdigitations, which are actually different cuts of the same structure. Na^+K^+ -activated ATPase is located near the lateral interdigitations.

(5). A variety of *intercellular junctions* have been described which connect adjacent cells within each epithelial layer, as well as the apical surfaces of the two layers.⁶ Tight junctions create a perme-

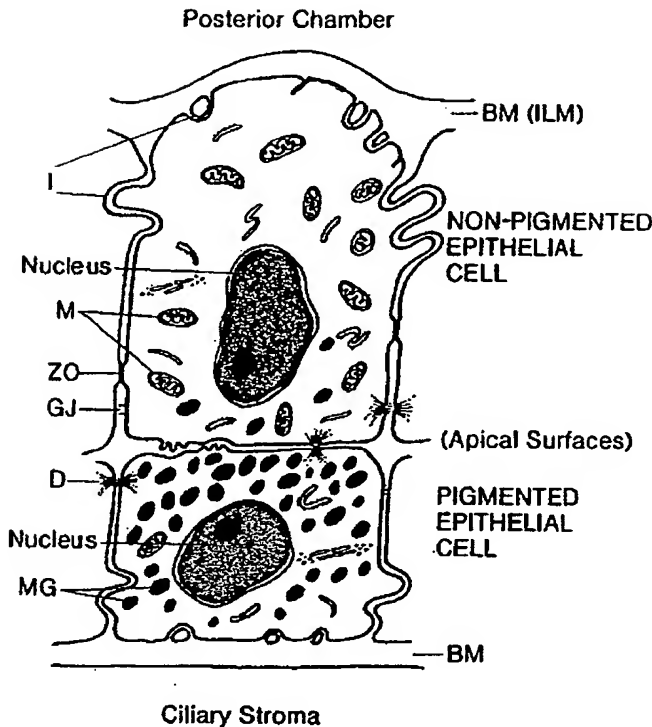


Figure 2.4. The two layers of ciliary epithelium are arranged with their apical surfaces in apposition to each other. Basement membrane (BM) lines the double cell layer and constitutes the internal limiting membrane (ILM) on the inner surface. The non-pigmented epithelium is characterized by mitochondria (M), zonula occludens (ZO), and lateral and surface interdigitations (I), while the pigmented epithelium contains numerous melanin granules (MG). Other intercellular junctions include desmosomes (D) and gap junctions (GJ).

ability barrier between the non-pigmented epithelial cells, which forms part of the *blood-aqueous barrier*. These tight junctions are said to be the "leaky" type, in contrast to the "non-leaky" type in the blood-retinal barrier, and may be the main diffusional pathways for water and ion flow.⁷

c. Microvilli separate the two layers of epithelial cells. In addition, "ciliary channels" have been described as spaces between the two epithelial layers. They are felt to be related to the formation of aqueous humor, since they develop between the fourth and sixth months of gestation, corresponding to the start of aqueous produc-

C. Theories of Aqueous Humor Production

1. Aqueous humor appears to be derived from *plasma* within the capillary network of the ciliary processes. To reach the posterior

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chamber, therefore, the various constituents of aqueous must traverse the three tissue layers of the ciliary processes; i.e., the capillary wall, stroma, and epithelia. The principal barrier to transport across these tissues is the *cell membrane* and related junctional complexes, and substances appear to pass through this structure by one of three mechanisms⁸:

a. *Diffusion*. Lipid-soluble substances are transported through the lipid portions of the membrane proportional to a concentration gradient across the membrane.

b. *Ultrafiltration*. Water and water-soluble substances (limited by size and charge) flow through theoretical "micropores" in the protein of the cell membrane in response to an osmotic gradient or hydrostatic pressure.

c. *Active transfer (secretion)*. Water-soluble substances of larger size or greater charge are actively transported across the cell membrane. This mechanism is believed to be mediated by globular proteins in the membrane and requires the expenditure of energy.

2. All three transport mechanisms are probably involved in aqueous production, possibly in accordance with the following *simplified three-part scheme*:

a. Tracer studies suggest that most *plasma* substances pass easily from the capillaries of the ciliary processes, across the stroma, and between the pigmented epithelial cells before accumulating behind the tight junctions of the non-pigmented epithelium.^{10, 11} This movement takes place primarily by *ultrafiltration*, and drugs that alter ciliary perfusion may exert their influence on intraocular pressure at this level.¹²

b. The tight junctions between the non-pigmented epithelial cells create part of the blood-aqueous barrier, and certain substances appear to be *actively transported* across this barrier into the posterior chamber, thereby establishing an osmotic gradient. Substances that are involved in active transport include:

(1). *Sodium*. There is a specific secretory pump for sodium,^{13, 14} and approximately 70% of this electrolyte is actively transported into the posterior chamber,¹⁵ while the remainder enters by passive ultrafiltration⁹ or diffusion.¹⁵ The active transport of sodium is ATPase-dependent,¹⁶ but does not appear to be related to the concentration of sodium in the plasma.¹⁷

(2). *Chloride*. A much smaller percentage of the chloride ion is actively transported, and this appears to be dependent on the presence of sodium, as well as pH.^{18, 19}

(3). *Potassium* is transported by secretion and diffusion.²⁰

(4). *Ascorbic acid* is secreted against a large concentration gradient.¹⁵

(5). *Amino acids* are secreted by at least three carriers.²¹

(6). *Bicarbonate*. The rapid interconversion between bicarbonate and CO₂, which is catalyzed by *carbonic anhydrase*, makes it difficult to determine the relative proportions of these two substances.

However, bicarbonate formation has been shown to influence fluid transport through its effect on sodium,²² possibly by regulating the pH for optimum active transport of sodium.⁹

c. *The osmotic gradient* across the ciliary epithelium, which results from the active transport of the above substances, leads to the movement of other plasma constituents by ultrafiltration and diffusion. There is evidence that sodium is the ion primarily responsible for the movement of water into the posterior chamber.^{13, 23}

3. *The precise location* of aqueous humor production appears to be predominantly in the anterior portion of the pars plicata along the tips or crests of the ciliary processes, and the site of active transport is in the non-pigmented epithelial cells probably in the cell membrane of the lateral interdigitations. The following observations support this concept.

a. *The anterior portion of the pars plicata* has 1) increased basal and lateral interdigitations, mitochondria, and rough endoplasmic reticulum in the non-pigmented ciliary epithelium, 2) more numerous fenestrations in the capillary endothelium and 3) a thinner layer of ciliary stroma.²⁴

b. When sodium fluorescein is administered systemically and the ciliary body is observed with a special gonioprism, fluorescein-stained aqueous is seen primarily at the tips of the ciliary processes.²⁵ In addition, an increase in cell organelles, fenestrations of capillary endothelium, and gap junctions between pigmented and non-pigmented epithelia has been observed at the crests of the ciliary processes.²⁵

c. Evidence of active transport in the non-pigmented epithelial cells, especially in the cell membrane of the lateral interdigitations, comes from observations of the following in these areas:

- (1). Abundant Na^+K^+ -activated ATPase.
- (2). Higher specific activity for glycolytic enzymes.²⁷
- (3). Preferential incorporation of labeled sulfate into macromolecules (primarily glycolipids and glycoproteins).^{28, 29}

D. Rate of Aqueous Humor Production

1. *Values.* The rate at which aqueous humor is formed (inflow) is measured in microliters per minute. The actual volume in the human eye varies somewhat according to the measurement technique used. A figure of approximately $2.0 \mu\text{l}/\text{min}$ is generally quoted,¹⁵ although fluorophotometric studies, which may provide the most reliable estimates, give a value of approximately $2.5 \mu\text{l}/\text{min}$ in the undisturbed human eye.³⁰

2. *Measurement techniques.* Tonography will be discussed in detail later in this chapter. The following is a brief overview of some of the more direct ways of estimating the rate of aqueous production:

a. *Fluorescein techniques* involve instillation of fluorescein into the anterior chamber by iontophoresis with subsequent measurement of either 1) the flow of unstained aqueous from the posterior to

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anterior chamber using *photogrammetric* methods³¹ or 2) the change in concentration of fluorescein in the anterior chamber by *fluorophotometry*.^{30, 32-35}

b. *Radioactive-labeled isotopes* have been used to measure inflow in animals by observing either 1) the *accumulation* of the isotope in the anterior chamber³⁶ or 2) the *decay rate* of the intracamerally injected isotope.³⁷

c. *Perfusion* of eyes at a constant pressure can also be used to determine the inflow in animals.³⁸

3. Many factors influence the rate of aqueous production, including the following:

a. *Intraocular pressure*

(1). An *elevation* of intraocular pressure is associated with a decline in aqueous production, which is referred to as *pseudofacility*.³⁹⁻⁴⁵

(2). A *decrease* in intraocular pressure may be associated with a transient increase in aqueous production.⁴³

b. *Age*. Fluorophotometric studies agree with the traditional concept that aqueous production decreases with age,³⁰ although the degree of this change is less than previously thought.⁴⁶ The formation of aqueous humor is actually much more stable than the intraocular pressure or anterior chamber volume with respect to aging changes.³⁰

c. *Inflammation* (uveitis) causes a *decrease* in inflow,^{47, 48} possibly related to a disruption in ciliary epithelium.⁴⁹

d. *Retinal detachment* is commonly associated with a reduction in the intraocular pressure. Whether this is due to a decrease in aqueous production, as has been suggested,⁵⁰ or an increase in aqueous outflow by an unconventional, posterior route, has yet to be determined.

e. Pharmacologic agents that reduce inflow are discussed in Section Three.

IV. FUNCTION AND COMPOSITION OF AQUEOUS HUMOR

A. Function^{15, 21, 51}

In addition to its role in maintaining a proper intraocular pressure, aqueous humor has important metabolic requirements in providing substrates and removing metabolites from the avascular cornea and lens. For example, the cornea takes glucose and oxygen from the aqueous and releases lactic acid and a small amount of carbon dioxide into the aqueous.^{15, 51} The lens also uses glucose and generates lactate and pyruvate.¹⁵ In addition, it is reported that potassium and amino acids in the aqueous may be taken up by the lens, while sodium moves from the lens to the aqueous.²¹ The metabolism of the vitreous and retina also appears to be associated with the aqueous humor in that substances such as amino acids and glucose pass into the vitreous from the aqueous.^{15, 21}

B. Composition

From the above discussion, it may be seen that the composition of aqueous humor depends not only on the nature of its production, but

also on the constant metabolic interchanges that occur throughout its intraocular course. However, close similarities in aqueous composition between the phakic and aphakic eye of the same individual suggest that lens metabolism has practically no influence on the composition of aqueous.⁵² Diffusional exchange across the iris may be a more significant factor in the changing composition of the aqueous between the posterior and anterior chambers. Studies in rabbit eyes indicate that the total concentration of dissolved substances, pH, and osmotic pressure are the same in the posterior and anterior chambers, while the actual composition of the aqueous in the two chambers is different.⁵³ This difference appears to be related to active transport in the posterior chamber and passive transfer in the anterior chamber, where the iris vessels are permeable to anions and nonelectrolytes.⁵³

The following statements describe only the general character of aqueous humor, expressed relative to plasma⁵¹⁻⁵⁷:

1. Aqueous of both the anterior and posterior chamber is slightly hypertonic compared to plasma.
2. Aqueous is acidic, with a pH in the anterior chamber of 7.2.⁵⁵
3. The two most striking characteristics of aqueous humor are:
 - a. A marked excess of ascorbate, which is fifteen times greater than that of arterial plasma.
 - b. A marked deficit of protein (0.02% in aqueous as compared to 7% in plasma). The albumin/globulin ratio is the same as plasma, although there is less gamma globulin. Human aqueous has been found to contain IgG, but no IgD, IgA, or IgM.⁵⁸ Protein and antibodies in the aqueous equilibrate with those in plasma to form a *plasmoid aqueous* under certain circumstances, including:
 - (1). *Uveitis*. Rabbit studies suggest the increased aqueous protein may come from proliferating blood vessels in the posterior chamber and vitreous and from disrupted, scarred ciliary epithelium.⁴⁹
 - (2). *Paracentesis*. Following aspiration of aqueous, the newly formed fluid has a high protein content, which is suggested by monkey studies to result from^{59, 60}:
 - (a). Blood reflux into Schlemm's canal with new gaps in the inner wall endothelial lining.
 - (b). Enlarged extracellular spaces in the ciliary epithelium of the anterior pars plicata.
4. The relative concentrations of free amino acids in the human aqueous varies, with aqueous/plasma concentrations ranging from 0.08 to 3.14; supporting the concept of active transport of amino acids.⁶¹
5. The concentrations of most other ions and nonelectrolytes are very close to those in the plasma, and conflicting statements in the literature primarily represent differences with regard to species and measurement techniques. In general, human aqueous has a slight excess of chloride and a deficiency of bicarbonate.^{55, 56} However, several factors lead to rapid changes in aqueous bicarbonate levels,

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and the concentrations measured may not accurately reflect the relative concentration of bicarbonate transported by the ciliary epithelia. Lactic acid is reported to be in relative excess in human aqueous⁵⁶; however, this determination varies widely with the technique of measurement.⁶² Glucose⁵⁶ and sodium⁵⁴ show a relative deficiency in the aqueous, although the latter is based on rabbit studies.⁵⁴ The total CO₂ content in aqueous has considerable species variation, with a deficiency in man.⁶³

V. AQUEOUS OUTFLOW

A. Histology of the Aqueous Outflow System

1. *Scleral Spur-roll*. The posterior wall of the scleral sulcus is formed by a group of fibers, the *scleral roll*, which run parallel to the limbus and project inward to form the *scleral spur* (Fig. 2.1).⁶⁴ The scleral spur-roll is composed of 75 to 80% collagen and 5% elastic tissue.⁶⁵ It has been suggested that this circular structure prevents the ciliary muscle from causing Schlemm's canal to collapse.⁶⁴

2. *Schwalbe's line*. Just anterior to the apical portion of the trabecular meshwork is a smooth area, which varies in width from 50 μ to 150 μ and has been called *Zone S*.⁶⁶ The anterior border of this zone is represented by the transition from trabecular to corneal endothe-

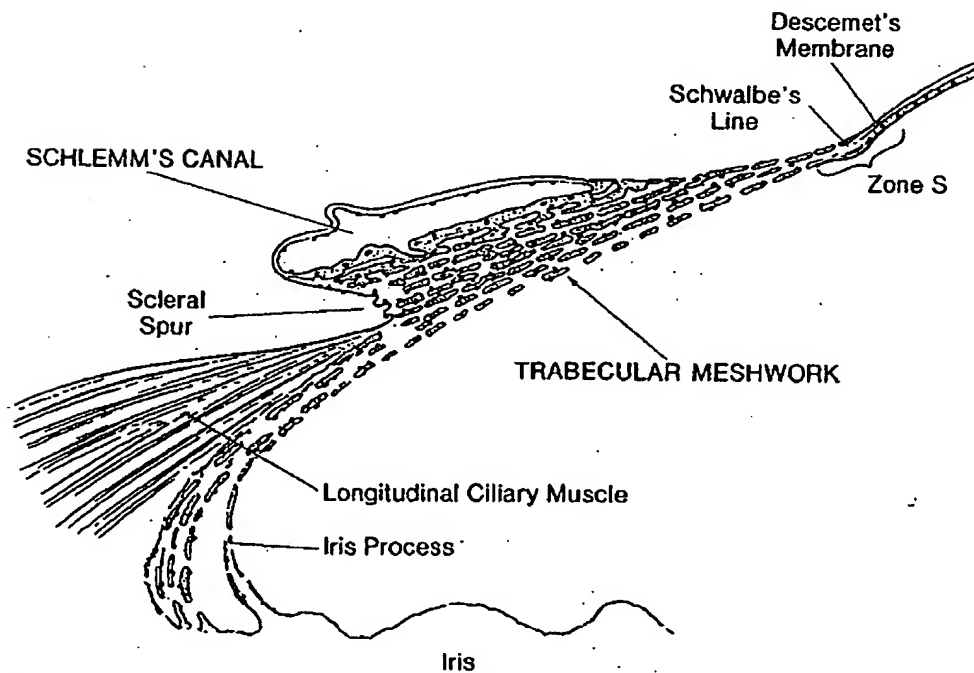


Figure 2.5. The trabecular meshwork extends from iris, ciliary body, and scleral spur to the sloping anterior wall of the scleral sulcus, converting the latter structure into Schlemm's canal.

lium and the thinning and termination of Descemet's membrane. The posterior border is demarcated by a discontinuous elevation, Schwalbe's line, that appears to be formed by the oblique insertion of uveal trabeculae into limbal stroma.⁶⁶

3. *Trabecular meshwork* (Figs. 2.5 and 2.6). As previously discussed, the scleral sulcus is converted into a circular channel, Schlemm's canal, by the trabecular meshwork. This tissue consists of a connective tissue core surrounded by endothelium, and may be divided into three portions.^{66, 67} (The ultrastructural details of these tissues will be considered later in this chapter.)

a. *The uveal meshwork*, the portion adjacent to the aqueous in the anterior chamber, is arranged in bands or rope-like trabeculae that extend from the iris root and ciliary body to the peripheral cornea. It is felt to be the oblique insertion of these trabecular bands into underlying limbal stroma that gives rise to the previously discussed Schwalbe's line.⁶⁶ The arrangement of the trabecular bands creates irregular openings that vary in size from 25 μ to 75 μ across.⁶⁷

TRABECULAR MESHWORK

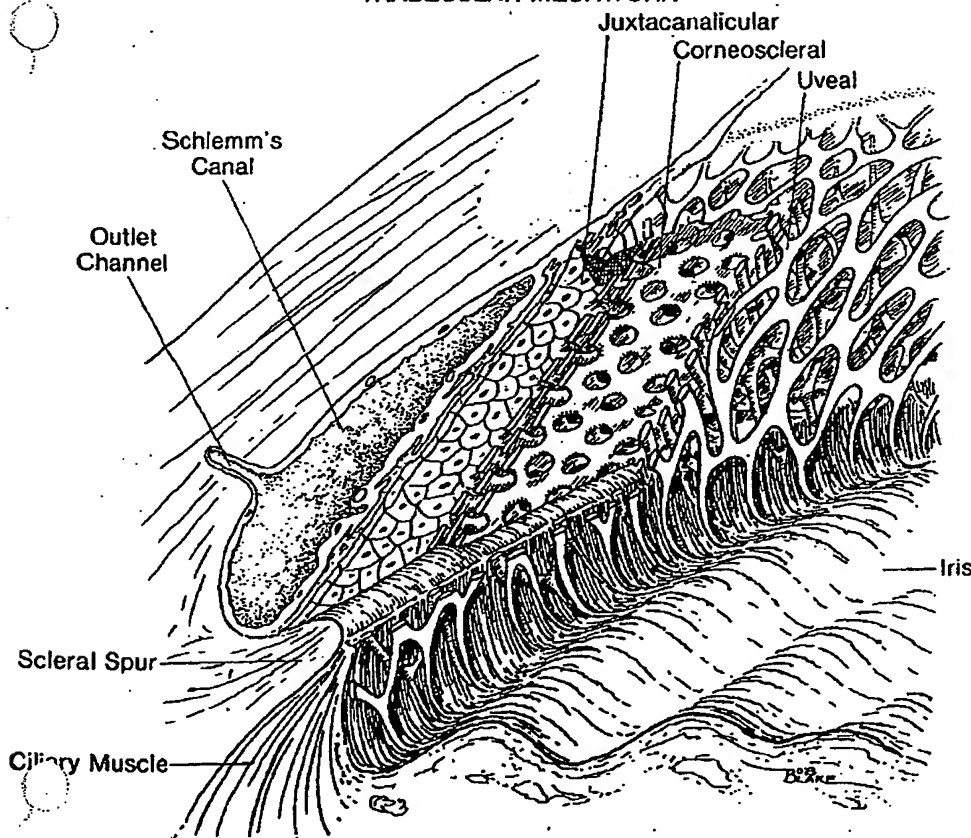


Figure 2.6. The trabecular meshwork is composed of three layers (shown in cut-away views): (1) uveal; (2) comeoscleral; and (3) juxtacanalicular.

b. The *corneoscleral meshwork* extends from the scleral spur to the lateral wall of the scleral sulcus and consists of sheets of trabeculae that are perforated by elliptical openings. These holes become progressively smaller as the trabecular sheets approach Schlemm's canal, with a range of $5\ \mu$ to $50\ \mu$ in diameter.⁶⁷

c. The *juxtacanalicular tissue*⁶⁸ is the outermost portion of the meshwork (adjacent to Schlemm's canal) and consists of a layer of connective tissue lined on either side by endothelium. The outer endothelial layer comprises the inner wall of Schlemm's canal, while the inner layer is continuous with the remainder of the trabecular endothelium.

4. *Schlemm's canal* is an endothelial-lined channel averaging 190 to 370 μ in diameter.^{69, 70} It may be a single channel, but occasionally branches into a plexus-like system.

5. *Intrascleral channels*. Schlemm's canal is connected to episcleral and conjunctival veins by a complex system of vessels (Fig. 2.7):

a. Intrascleral aqueous vessels, the *aqueous veins of Ascher*,⁷¹ have been defined as originating at the outer wall of Schlemm's canal and terminating in episcleral and conjunctival veins in a laminated

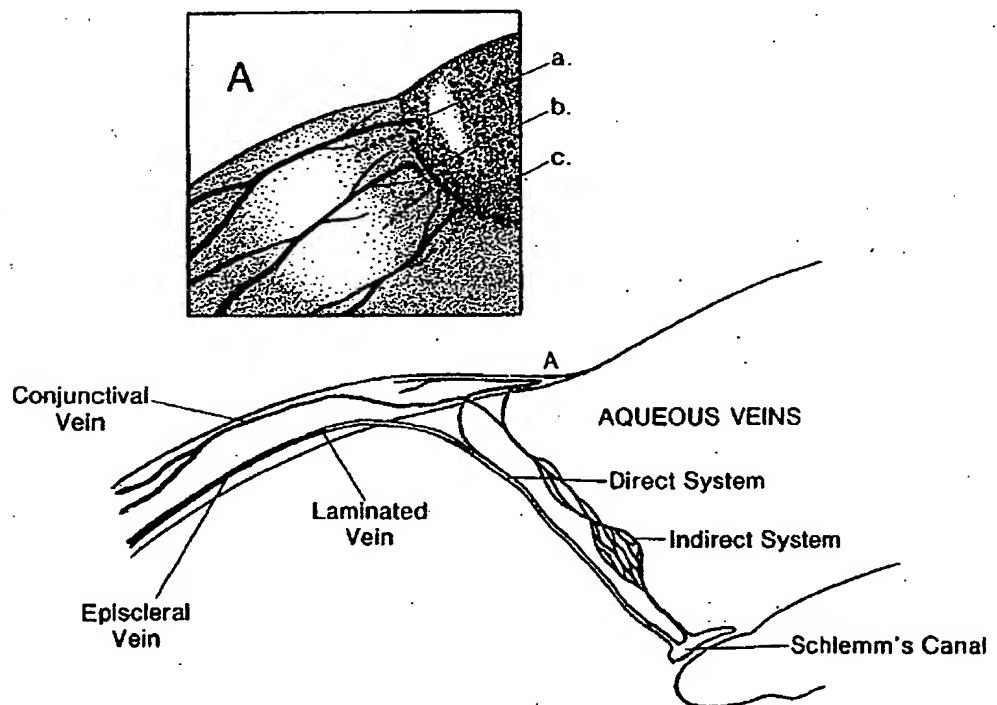


Figure 2.7. Intrascleral channels drain aqueous by direct and indirect (plexus) systems from Schlemm's canal to episcleral and conjunctival veins. Inset (A) shows three courses of anteriorly-directed veins: a: short course into cornea, b: short course parallel to limbus (most common pattern), and c: sharp loop at limbus.

junction, referred to as the "laminated vein of Goldmann."⁷² However, others refer to the proximal portion of these vessels as "outflow channels"^{70, 73} or "collector channels,"⁶⁹ since the structural pattern of the outer wall of Schlemm's canal extends into the first third of these channels.⁷³ The intrascleral vessels are divided into two systems:^{69, 70, 73-75}

(1). A *direct* system. Large caliber vessels run a short intrascleral course and drain directly into the episcleral venous system.

(2). An *indirect* system. More numerous, finer channels form an intrascleral plexus before eventually draining into the episcleral venous system.

b. The intrascleral aqueous channels do not connect with vessels of the uveal system, except for occasional fine communications with the ciliary muscle.⁷⁴⁻⁷⁶ There are no arterial communications,⁷⁴⁻⁷⁶ although arteriovenous anastomotic vessels may occur in the anterior episcleral system.⁷⁴⁻⁷⁷

c. The aqueous vessels join the *episcleral venous system* by several routes⁷¹:

(1). Most aqueous vessels are directed *posteriorly* with the majority of these draining into episcleral veins, while a few cross the subconjunctival tissue and drain into conjunctival veins.

(2). Some aqueous vessels proceed *anteriorly* to the limbus, with most of these running a short course parallel to the limbus before turning posteriorly to conjunctival veins. Other vessels make a sharp loop to join conjunctival veins or rarely extend a short distance into the cornea before turning posteriorly.

6. The *episcleral veins* drain into the cavernous sinus via the anterior ciliary and superior ophthalmic veins, while the *conjunctival veins* drain into superior ophthalmic or facial veins via the palpebral and angular veins.⁷²

7. *Extracanalicular (uveoscleral) outflow pathways*. The pathways described above are estimated to account for between 83⁷⁸ and 96%⁷⁹ of aqueous outflow in human eyes under normal circumstances. The other 5 to 15% of the aqueous leaves the eye by a system, or systems, that have been collectively called "uveoscleral,"⁷⁹⁻⁸¹ "uveo-vortex,"⁸² "unconventional,"⁸³ or "secondary"⁸⁴ aqueous outflow pathways. The variety of names testifies to our incomplete understanding regarding this segment of the aqueous outflow system. Brubaker (personal communication) suggested the logical terms "canalicular" for the principal outflow pathway, involving Schlemm's canal, and "extracanalicular" for the other channels of aqueous outflow.

Although there is no universal agreement as to the anatomy of the extracanalicular outflow pathways, tracer studies in human⁷⁹ and animal⁸⁰⁻⁸⁴ eyes suggest that the aqueous enters the stroma and vessels of the iris and ciliary body and then moves posteriorly, either through the suprachoroidal or choroidal vessels, to leave the eye through scleral pores surrounding long posterior ciliary arteries and nerves, or in vortex veins or vessels of optic nerve membranes.

B. Ultrastructure of Trabecular Meshwork and Schlemm's Canal

1. *Uveal and corneoscleral meshwork.* Although the gross structure of these two trabecular subunits differs, as previously discussed, their ultrastructure is the same. Each trabecular band or sheet is composed of *four concentric layers*⁸⁵:

a. An *inner connective tissue core* is composed of typical collagen fibers, with the usual 640 Å periodicity.⁸⁵

b. "Elastic" fibers are actually composed of otherwise typical collagen, arranged in a spiraling pattern with an apparent periodicity of 1,000 Å.^{86, 87}

c. Between the spiraling collagen and the basement membrane of the endothelium is a broad zone composed of delicate filaments embedded in a ground substance.⁸⁶ This layer has been called a *glass membrane*.⁸⁵

d. An *endothelial layer* provides a continuous covering over the trabeculae. The cells are larger, more irregular, and have less prominent borders than corneal endothelial cells.⁶⁶ Characteristics of trabecular endothelium include the following.

(1). *Phagocytic activity.* The cells have been shown to engulf and degrade foreign material,⁸⁸ or to engulf debris, detach from the trabecular core, and leave in Schlemm's canal.⁸⁹

(2). *Microfilaments.* Two types of filaments have been found in the cytoplasm of human trabecular endothelium⁹¹:

(a). 6 nm filaments are located primarily in the cell periphery, around the nucleus, and in cytoplasmic processes. These appear to be *actin filaments*⁹¹ which are involved in 1) cell contraction and motility, 2) phagocytosis and pinocytosis, and 3) cell adhesion (the possible role in resistance to outflow will be discussed later in this chapter).

(b). 10 nm filaments are more numerous in the cells and probably play a structural role.

(3). Preliminary reports show that the metabolism of trabecular meshwork tissue can be studied with biochemical techniques,⁹² and that trabecular cells can be grown in tissue culture,⁹³ both of which may be useful approaches to further our understanding of this tissue in normal and disease states.

2. *Juxtacanalicular Tissue.* The portion of the trabecular meshwork adjacent to Schlemm's canal (and which actually makes up the inner wall of the canal) differs histologically from the other parts of the meshwork and has been given various names, depending on how one defines the anatomical limits of the tissue: "juxtacanalicular connective tissue,"⁶⁸ "pore tissue,"⁶⁷ and "endothelial meshwork."⁹⁴ In the broadest sense, this structure has *three layers*,⁹⁵ discussed here beginning with the innermost portion (Fig. 2.8).

a. A *trabecular endothelial layer* is continuous with the endothelium of the corneoscleral meshwork and might be considered as a part of this layer.

b. A *central connective tissue layer* of variable thickness is

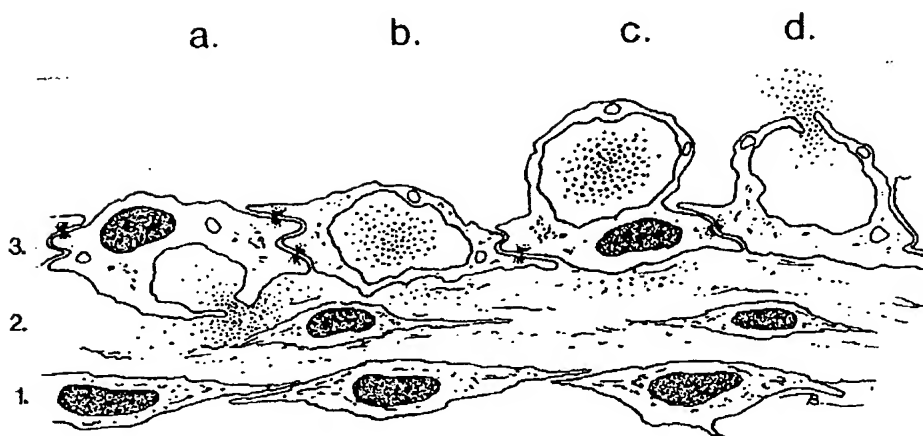


Figure 2.8. The juxtacanalicular portion of the trabecular meshwork, by the broadest definition, is composed of three layers: 1: Trabecular endothelium, continuous with the corneoscleral meshwork; 2: a central connective tissue layer; and 3: the inner wall endothelium of Schlemm's canal. The theory of transcellular aqueous transport is depicted, in which a series of pores and giant vacuoles open on the connective tissue side (a), engulf aqueous (b), bulge into Schlemm's canal (c), and open to release aqueous into the canal (d).

unfenestrated and has several layers of parallel, spindle-shaped cells loosely arranged in a connective tissue ground substance.^{68, 86, 95}

c. The *inner wall endothelium of Schlemm's canal* is also the outermost portion of the trabecular meshwork, i.e., the last tissue that aqueous must traverse before entering the canal. This endothelial layer has significant morphological characteristics, which distinguish it from the rest of the endothelium in both the trabecular meshwork and in Schlemm's canal.

(1). The *surface* is bumpy due to protruding nuclei,⁹⁵ cyst-like vacuoles,⁹⁶ and finger-like projections⁹⁷ bulging into the canal. Johnstone⁹⁷ has shown that the finger-like projections are endothelial tubules with patent lumens, communicating between the anterior chamber and Schlemm's canal. Svedbergh,⁹⁸ however, interpreted them as protrusions with no significant openings. Further study will be needed to determine the significance of these structures.

(2). *Actin filaments*, as previously described in uveal and corneoscleral trabecular endothelium, are also present in the inner wall endothelium of Schlemm's canal.⁹¹

(3). The *intercellular spaces* are 150 to 200 Å wide and the adjacent cells are connected by a variety of intercellular junctions.^{88, 95} It is not clear as to how tightly these junctions maintain the intercellular connections, although it has been shown that they will open to permit the passage of red blood cells.⁹⁵

(4). The endothelial cells are anchored by cytoplasmic processes to underlying subendothelial cells and trabecular meshwork.⁹⁹

(5). *Openings* in the endothelial cells have been described by

many investigators. Considerable controversy has arisen as to the morphology and function of these structures. In general, the openings consist of *minute pores* and large, or *giant, vacuoles*. The reported sizes of the pores vary considerably, although most are in the range of 0.5 to 2.0 μ .^{67, 69, 100-106} Tracer studies have shown that these pores communicate with the intertrabecular spaces and Schlemm's canal.^{104, 105} The giant vacuoles in the endothelial cells were once felt to be postmortem artifacts,¹⁰⁷ but numerous studies have confirmed their existence and suggested that they are involved in aqueous outflow.^{94, 108-112} It may be that the pores and vacuoles represent different parts of the same transcellular channels.¹⁰⁴ The possible significance of these structures in resistance to aqueous outflow will be discussed later in this chapter.

(6). Sonderman's "canals" are mentioned primarily for historical interest, and because the term may still be found in the literature. Although they were originally described as endothelial-lined channels communicating between the canal and intertrabecular spaces,¹¹³ subsequent studies have variably interpreted them as tortuous communications wandering irregularly and obliquely through the meshwork,¹¹⁴ deep grooves on cross-section,⁹⁴ slit-like spaces between cells,^{115, 116} or artifacts.⁶⁷ It is unlikely that the structures, if they exist, have a significant role in aqueous outflow.

3. The Outer Wall of Schlemm's Canal

a. The endothelium of the outer wall is a single cell layer that is continuous with that of the inner wall.⁸⁶ The surface is smoother than that of the inner wall and has larger, less numerous cells¹¹⁷ and no pores,^{100, 101} but numerous, large *outlet channels*, as previously described.

b. Torus or lip-like thickenings have been observed around the openings of the outlet channels^{70, 73} and septae have been noted to extend from these openings to the inner wall of Schlemm's canal, which presumably help to keep the canal open.^{69, 70, 73}

c. The endothelium is separated from the collagenous bundles of the limbus by a basement membrane⁸⁶ and layers of fibrocytes and fibroblasts.⁷³

C. Normal Resistance to Aqueous Outflow

1. *Trabecular meshwork and Schlemm's canal.* Grant^{118, 119} demonstrated that a 360° incision in the trabecular meshwork of non-glaucomatous, enucleated human eyes eliminated 75% of the resistance to aqueous outflow. Whether this resistance is in the meshwork or is due to compression of Schlemm's canal is uncertain, but the following observations have been reported:

a. *Inner wall endothelium of Schlemm's canal.* Studies with tracer elements such as ferritin or thorotrast, suggest free flow through the trabecular spaces and juxtacanalicular connective tissue with heavy accumulation of the tracer on the inner surface of the inner wall endothelium of Schlemm's canal.^{95, 104, 105, 110} This endothelial layer, therefore, appears to provide some degree of resistance to

outflow, and the mechanism of transport across the layer is only partially understood:

(1). Pores and giant vacuoles in the inner wall endothelium of Schlemm's canal, as previously discussed, appear to be parts of a transcellular system for aqueous outflow, since tracer elements injected into the anterior chamber are seen in the vacuoles and pores.^{95, 104, 105, 110, 120} The observation that the concentration of tracer material in the giant vacuoles is not always the same as in the juxtacanalicular connective tissue⁹⁵ suggests a dynamic system in which the vacuoles intermittently open and close to transport aqueous from the juxtacanalicular tissue to Schlemm's canal (Fig. 2.8).¹¹⁰ Whether this transport is active or passive has been controversial.

(a). Indirect evidence for a theory of active transport has included the demonstration of enzymes¹²¹ and electron microscopic structures¹²² compatible with an active transport system in or near the endothelial layer.

(b). However, the bulk of evidence supports the theory of passive (pressure-dependent) transport, since the number and size of vacuoles has been shown to increase with progressive elevation in the intraocular pressure.¹²³⁻¹²⁶ Furthermore, this phenomenon is reversible in the enucleated eye,¹²⁴ and hypothermia has no effect on the development of the vacuoles in the enucleated eye¹²⁷ and only little effect on outflow in the eyes of living rabbits.¹²⁸

It may be, therefore, that potential transcellular spaces exist in the inner wall endothelium of Schlemm's canal, which open as a system of vacuoles and pores, primarily in response to pressure, to transport aqueous from the juxtacanalicular connective tissue to Schlemm's canal (Fig. 2.8). The actual resistance to aqueous outflow provided by this system is unclear, although it has been calculated, based on the estimated size and total number of pores in the inner wall endothelium of Schlemm's canal, that resistance to outflow through the endothelial cells is a small fraction of the total resistance to outflow.¹²⁹

(2). Contractile microfilaments, as previously described, occur in the inner wall endothelium of Schlemm's canal, as well as the endothelium lining the trabeculae. Perfusing monkey eyes with substances that are known to disrupt the microfilaments, such as cytochalasin B¹³⁰⁻¹³² or EDTA,^{133, 134} significantly reduces the resistance to aqueous outflow, and histologic studies suggest that this is primarily due to an alteration in the trabecular meshwork or inner wall of Schlemm's canal.¹³¹⁻¹³⁴

(3). Fibrinolytic activity has been demonstrated in the endothelium of Schlemm's canal,¹³⁵ but no evidence of coagulation factors has been found.¹³⁶ This suggests that a hemostatic balance, displaced towards fibrinolysis, protects this portion of the outflow system from occlusion by fibrin and platelets.^{135, 136}

b. Acid mucopolysaccharides that are sensitive to hyaluronidase have been demonstrated in various portions of the trabecular meshwork.¹³⁷⁻¹³⁹ In the polymerized form, mucopolysaccharides become

hydrated, which may lead to increased resistance to outflow by closure of the trabecular spaces.¹³⁹ Enzymes that catabolize mucopolysaccharides have been demonstrated in the meshwork,¹⁴⁰ and these enzymes may be released by lysosomes to depolymerize the mucopolysaccharides, thereby minimizing this cause of resistance to outflow.^{139, 140} In support of this theory, perfusion of eyes with hyaluronidase has been shown to increase outflow facility^{119, 141} and increase the number of giant vacuoles.¹⁴² In addition, prolonged perfusion of canine eyes caused a gradual increase in outflow facility, apparently due to a "washout" of a hyaluronidase-sensitive component of the barrier to aqueous outflow.^{143, 144} However, perfusion studies with enucleated monkey eyes, using a trabeculotomy and hyaluronidase, suggest that resistance by mucopolysaccharides is only slightly related to the trabecular meshwork.¹⁴⁵

c. *Resistance in Schlemm's Canal.* Once aqueous has entered Schlemm's canal, resistance to continued flow into the intrascleral outlet channels may depend on the spatial configuration of the canal.

(1). There is controversy as to whether the canal is normally entirely open and whether it allows *circumferential flow*. Perfusion studies in enucleated human adult eyes suggest that aqueous cannot flow more than 10° within the canal,¹⁴⁶ although there is less resistance to circumferential flow in infant eyes.¹⁴⁷ However, studies of segmental blood reflux into Schlemm's canal imply that the canal is normally entirely open and that there is circumferential flow.¹⁴⁸

(2). *Elevation of intraocular pressure* is known to be associated with increased resistance to outflow,¹⁴⁹⁻¹⁵¹ which may be a result of collapse of Schlemm's canal.¹⁵² Histologic studies of eyes perfused at different pressures suggest that compromise of the canal lumen with elevated intraocular pressure is due to distention of the trabecular meshwork,^{153, 154} an increase in endothelial vacuoles,¹²³⁻¹²⁶ and a ballooning of the inner wall endothelial cells into the canal.⁹⁹ Perfusion studies also suggest the resistance to aqueous outflow may normally depend in part on an intact, unyielding outer wall of Schlemm's canal, against which the intact inner wall is pressed by the intraocular pressure.¹⁵⁵ However, significant differences in the response to elevated perfusion pressure have been found among different mammalian eyes, and it has been suggested that factors other than, or in addition to, collapse of Schlemm's canal may be important regarding the influence of elevated intraocular pressure on resistance to outflow.¹⁵⁶

(3). A *reduction in normal resistance to outflow* occurs with a widening of Schlemm's canal. Moses and Arnzen¹⁵⁷ have described the trabecular meshwork as a three-dimensional set of diagonally crossing collagenous fibers, which respond to a backward, inward displacement with a widening of Schlemm's canal. The effect of this form of traction on the meshwork has been demonstrated with deepening of the anterior chamber during perfusion studies when an iridectomy is not made,¹¹⁸ posterior depression of the lens,^{146, 158} or tension on the choroid.¹⁵⁹

2. *Intrascleral Outflow Channels.* The remainder of the resistance to aqueous outflow appears to be within the intrascleral outflow channels. One monkey study has suggested the following distribution of resistance¹⁵⁰:

- a. Trabecular meshwork: 60 to 65%
- b. Inner $\frac{1}{2}$ to $\frac{1}{2}$ of sclera: 25%
- c. Outer $\frac{1}{2}$ to $\frac{1}{2}$ of sclera: 15%

3. *Episcleral Venous Pressure.* The normal episcleral venous pressure is approximately 9 mmHg. Although this is not considered to be a part of resistance to outflow, it does contribute to the intraocular pressure. The precise interrelationship between episcleral venous pressure and aqueous humor dynamics is complex and only partially understood.

4. *Extracanalicular Outflow.* Unlike the canalicular (or conventional) outflow system, extracanalicular outflow has been reported to improve with an elevation of the intraocular pressure, presumably due to ultrafiltration of aqueous into uveal vessels.⁸⁰ It has also been shown that outflow by this route is reduced by miotics.⁷⁹ It should be noted that our understanding of the extracanalicular outflow system is based more on physiology than on anatomy, and further study is needed to correlate function and anatomy in this system.

VI. GONIOSCOPY

Gonioscopy is a clinical technique that is used to examine structures in the anterior chamber angle. Gonioscopic assessment is essential both for diagnosing the type of glaucoma and for planning the appropriate therapy, since the treatment for one type of glaucoma may be ineffective or contraindicated in another form. The subject is included in this chapter because of its relevance to the anatomy of aqueous humor dynamics. The present discussion, however, will be limited to technique and normal anatomic findings, while the alterations associated with the various forms of glaucoma will be considered in Section Two.

A. The Principle of Gonioscopy (Fig. 2.9)¹⁶¹

1. The problem is the critical angle

a. When light passes from a medium with a greater index of refraction (n) to one of a lesser n , the angle of refraction (r) will be larger than the angle of incidence (i). When r equals 90° , i is said to have attained the critical angle. When i exceeds the critical angle, the light is reflected back into the first medium.

b. The critical angle for the cornea-air interface is approximately 46° . Light rays coming from the anterior chamber angle exceed this critical angle and are, therefore, reflected back into the anterior chamber, preventing visualization of the angle.

2. The solution is to eliminate the cornea (optically).

Since the n of a contact lens approaches that of the cornea, there is minimal refraction at the interface of these two media, which eliminates the optical effect of the front corneal surface. Therefore,

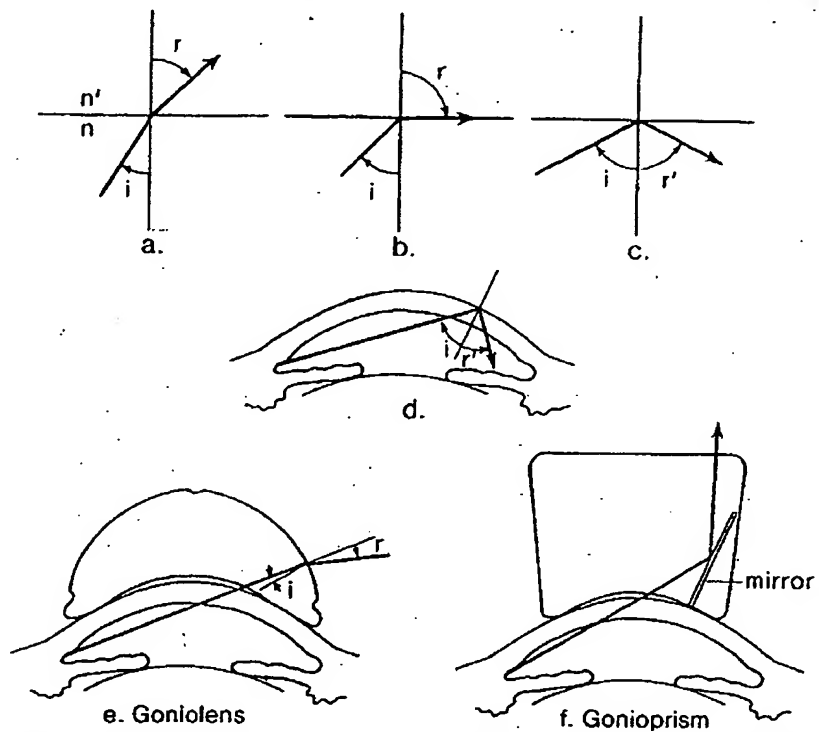


Figure 2.9. Principle of gonioscopy: a: Light ray is refracted when angle of incidence (i) at interface of two media with different indices of refraction (n and n') is less than the critical angle; b: Angle of refraction (r) is 90° when i equals the critical angle; and c: Light is reflected when i exceeds the critical angle. d: Light from anterior chamber angle exceeds the critical angle at the cornea-air interface and is reflected back into the eye; e and f: contact lenses have an index of refraction (n) similar to that of the cornea, allowing light to enter the lens and then be refracted (goniolens) or reflected (gonioprism) beyond the contact lens-air interface.

light rays from the anterior chamber angle enter the contact lens and are made to pass through the new contact lens-air interface by one of two basic designs¹⁶¹⁻¹⁶³:

a. In *direct gonioscopy*, the anterior curve of the contact lens (goniolens) is such that the critical angle is not reached, and the light rays are refracted at the contact lens-air interface.

b. In *indirect gonioscopy*, the light rays are reflected by a mirror in the contact lens (gonioprism) and leave the lens at nearly a right angle to the contact lens-air interface.

B. Instruments and Techniques

1. *Historical background.*¹⁶² In 1907, Trantas visualized the angle in an eye with keratoglobus by indenting the limbus and later coined the term, gonioscopy. Salsmann introduced the goniolens in 1914, and Koepe improved it 5 years later by designing a steeper lens.

Troncoso also contributed to gonioscopy by developing the gonioscope for magnification and illumination of the angle. In 1938, Goldmann introduced the gonioscope, and Barkan established the use of gonioscopy in the management of glaucoma.

2. Direct gonioscopy

a. Instruments¹⁶⁴

(1). The *Koepe lens* is the prototype diagnostic goniolens and is available in different diameters and radii of posterior curvature. Additional types of goniolenses are listed in table one.

(2). A gonioscope provides 15 to 20X magnification. It may be hand-held or suspended from the ceiling with counterbalance.

(3). The *light source* is usually a separate hand-held unit, such as the Barkan focal illuminator, although it may be attached to the gonioscope.

b. *Technique*. Direct gonioscopy is performed with the patient in a supine position, preferably on a moveable diagnostic table. After applying a topical anesthetic, the goniolens is positioned on the cornea, using a bridge of balanced salt solution, a viscous preparation, the patient's own tears.¹⁶⁵ The examiner usually holds the gonioscope in one hand and a light source in the other. Occasionally an assistant may be needed to move the goniolens to the desired position. Alternatively, a gonioscope with mounted light source may be used, which allows the examiner to control the goniolens with his other hand. In either case, the examiner scans the anterior chamber angle by shifting his position until all 360° have been studied.

Table 2.1
Contact Lenses for Gonioscopy

	Lens	Description/Use
I. Goniolenses (Direct Gonioscopy)	1. Koepe	1. Prototype diagnostic gonio- lens
	2. Richardson- Shaffer	2. Small Koepe lens for infants
	3. Barkan	3. Prototype surgical goniolens
	4. Siebeck	4. Tiny goniolens; floats on cor- nea
	5. Worst	5. Partial vacuum anchors lens to cornea
II. Gonioscopes (Indirect Gonioscopy)	1. Goldmann one- mirror	1. Prototype gonioscope
	2. Goldmann two- mirror	2. Both mirrors same as above
	3. Goldmann three- mirror	3. One mirror for gonioscopy; two for retina
	4. Zeiss four-mirror	4. All mirrors for gonioscopy; fluid bridge not required
	5. Allen-Thorp	5. Four gonioscopy mirrors; re- quires fluid bridge between lens and cornea
	6. Worst Lo-Vac	6. Six mirrors; held to cornea by vacuum

3. Indirect Gonioscopy

a. *Instruments.* The gonioscope and a slit lamp are the only instruments needed for indirect gonioscopy. The *Goldmann one-mirror lens* is the prototype gonioscope. The mirror in this lens has a height of 12 mm and the posterior radius of curvature of the gonioscope is 8.15 mm. A large variety of additional gonioscopes are available and are listed in table one.

b. *Technique.* The cornea is anesthetized and, with the patient positioned at the slit lamp, the gonioscope is placed against the cornea with or without a fluid bridge, depending on the posterior radius of curvature of the instrument. The lens is then rotated to allow visualization of all 360° of the angle or the quadrants are studied with the four mirrors. Although visualization of the angle can be enhanced by manipulating the gonioscope, e.g., asking the patient to look in the direction of the mirror being used, such maneuvers must be used with caution, since they can distort the appearance of the angle depth.¹⁶⁶ It has also been suggested that the Goldmann gonioscope can be used with a direct ophthalmoscope set at +10 or +20 when a slit lamp is not available.¹⁶⁷

4. *Comparison of Direct and Indirect Gonioscopy.* There is no unanimity of opinion as to which basic method of gonioscopy is best. Advantages have been suggested for both approaches:

a. With *direct gonioscopy*, the height of the observer may be changed to look deeper into a narrow angle, while the gonioscope is limited in this regard by the height of the mirror. In addition, the gonioscope may cause less distortion of the anterior chamber. Both features make it desirable when assessing the true depth of the anterior chamber angle.^{168, 169}

b. In *indirect gonioscopy*, the slit lamp may provide better optics and lighting, which could be an advantage when looking for subtle details in the angle.¹⁷⁰ Furthermore, the method requires less additional instrumentation and space (assuming the slit lamp is already a part of the routine office examination) and is probably faster than direct gonioscopy. The latter is particularly true of the Ziess four-mirror lens, which is useful for rapid screening.

To minimize the two major disadvantages of gonioscopes, newer designs have included a posterior radius of curvature closer to that of the anterior corneal surface to reduce corneal distortion^{168, 171} and taller mirrors to facilitate visualization of narrow angles.¹⁶⁸

C. Normal Appearance of Adult Anterior Chamber Angle

1. Starting at the root of the iris and progressing anteriorly toward the cornea, the following structures can be identified by gonioscopy in a normal open adult angle (Fig. 2.10)¹⁷²:

a. *The ciliary band* is that portion of the ciliary body which is visible in the anterior chamber as a result of the iris inserting into the ciliary body. The width of the band depends on the level of iris insertion, and tends to be wider in myopia and narrower in hyperopia. The color of the band is usually gray or dark brown.

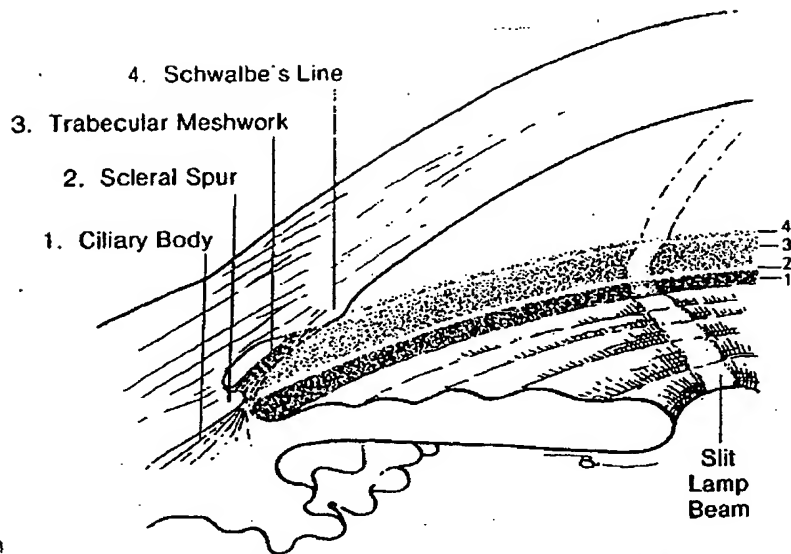


Figure 2.10. Normal appearance of adult anterior chamber angle, starting at the root of the iris and progressing anteriorly: 1: Ciliary body band; 2: Scleral spur; 3: Trabecular meshwork (degree of pigmentation varies); and 4: Schwalbe's line.

b. *The scleral spur* is the posterior portion of the scleral sulcus, which is attached to the ciliary body posteriorly and the corneoscleral meshwork anteriorly. It is usually seen as a prominent white line unless obscured by dense uveal meshwork or excessive pigment dispersion.

c. *The trabecular meshwork* is seen as a band just anterior to the scleral spur. It varies considerably in appearance, since it has no pigment at birth, but develops color with age from faint tan to dark brown, depending on the degree of pigment dispersion in the anterior chamber. The central one-third corresponds to the location of Schlemm's canal, where blood reflux may sometimes be seen as a red band.

d. *Schwalbe's line* marks the forward limit of the anterior chamber angle structures. It is a fine ridge just in front of the meshwork and is often identified by a small build-up of pigment, especially inferiorly.

2. *Blood vessels* are normally not seen in the angle, although loops from the major arterial circle may appear in front of the scleral spur and rarely over the meshwork. In addition, an anterior ciliary artery may occasionally be visible in the ciliary band of lightly pigmented eyes.

D. Recording Gonioscopic Findings

A variety of charts and classifications have been suggested for describing the observations made by gonioscopy. These will be

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discussed in Section Two, although descriptive words and drawings are probably the most useful technique. The drawings can be placed on a chart with concentric circles to represent the different parts of the anterior chamber angle, and the recorded data should include: 1) configuration of the angle, 2) degree of pigmentation, 3) presence of abnormal structures.

E. Cycloscopy^{25, 45}

This technique is similar to gonioscopy, but allows visualization of ciliary processes under special circumstances, such as the presence of an iridectomy, wide iris retraction, aniridia, and some cases of aphakia in association with limbal indentation. The main value of the technique thus far has been in research studies of the ciliary processes, although it may hold promise for diagnostic and therapeutic purposes.

VII. TONOGRAPHY

Tonography is a clinical, non-invasive technique for estimating the facility of aqueous outflow. It has been extremely valuable in advancing our understanding of the mechanisms of glaucoma and the actions of antiglaucoma drugs, although its clinical usefulness in the detection and management of glaucoma remains a matter of controversy. Nevertheless, it is worth considering tonography in some detail, since an understanding of the involved physiology provides insight into the complex interplay of factors related to aqueous humor dynamics.

A. Historical Background

1. The mathematics

a. *Poiseuille's law* (pronounced "pwah zoo' ez"). The 19th century French physician and physiologist, Poiseuille, pursued his interest in the circulation of blood by studying the flow of liquids in tubes of very small diameter.¹⁷³ This work led to the formulation of an equation that relates the velocity of flow (F) of fluid in a rigid tube to 1) the radius of the tube (r), 2) the pressure drop per length of tube ($P_1 - P_2/l$), and 3) the coefficient of viscosity (n) of the fluid¹⁷⁴:

$$F = \frac{\pi r^4}{8n} \cdot \frac{P_1 - P_2}{l}$$

b. In 1949, Goldmann sought to apply Poiseuille's law to aqueous outflow, suggesting that the rate of aqueous flow through the trabecular meshwork (F) is directly proportional to the intraocular pressure (P_o) minus the episcleral venous pressure (P_v) and inversely proportional to the resistance to outflow (R)¹⁷⁵:

$$F = \frac{P_o - P_v}{R}$$

The equation implied that aqueous flow in living ocular tissue could be expressed in the same linear terms as that of fluid in rigid

tubes, a belief that would subsequently be proven inaccurate. Nevertheless, it was modifications of Poiseuille's law that led to the mathematical foundation for tonography.

2. The technique¹⁷⁶

a. At approximately the same time that Poiseuille was conducting his studies, Pagenstecher (1878) observed that massage of the eye lowered the intraocular pressure. In 1905, Schiøtz reported that repeated tonometry also lowered the pressure, although less so in eyes with glaucoma.

b. Polak-van Gelder, applying the above observations, described a technique in 1911 of repeated tonometer applications for 1 to 2 minutes to differentiate normal and glaucomatous eyes. Schoenberg modified this technique the following year by using a continuous application of the tonometer while reading the pressure fall on the scale of the instrument.

3. In 1950, Grant¹⁷⁷ introduced the modern concept of tonography by combining a modification of Poiseuille's law with electronic techniques of continuous intraocular pressure measurement.

B. Mathematical Basis

1. Relationship of pressure to outflow

a. As Goldmann¹⁷⁵ suggested, the rate of aqueous outflow (F), which is expressed in $\mu\text{l}/\text{min}$, is proportional to the intraocular pressure (P_o), minus the episcleral venous pressure (P_v):

$$F \propto (P_o - P_v)$$

b. Grant^{177, 178} proposed that the factors which convert this proportionality to equality be expressed collectively as the coefficient of outflow facility (C), which is given in $\mu\text{l}/\text{min}/\text{mmHg}$:

$$F = C(P_o - P_v)$$

The C -value is an expression of the degree to which a change in the intraocular pressure will cause a change in the rate of aqueous outflow, which is an indirect expression of the patency of the aqueous outflow system.

2. Estimation of the C -value¹⁷⁷

a. Tonography is a means of estimating the C -value by raising the intraocular pressure with the weight of an indentation tonometer and observing the subsequent decay curve in the IOP. (This discussion presupposes an understanding of indentation tonometry, and the reader may wish to see the next chapter for an explanation of that technique.)

b. The weight of the tonometer plunger on the cornea raises the IOP from the baseline (P_o) to a new, higher level (P_t). The elevated pressure causes an increased rate of aqueous outflow, leading to a change in the aqueous volume (ΔV), which is inferred from Friedenwald's tables relating volume change to Schiøtz scale readings.¹⁷⁹

Direct measurements of intraocular fluid volume change in enucleated eyes have supported Friedenwald's calculations.¹⁸⁰ Assuming for

the moment that the elevated pressure does not alter other ocular parameters, the rate of volume decrease ($\Delta V/T$) equals the rate of outflow.

c. The standard tonographic technique is to measure the IOP for 4 minutes, i.e., $T = 4$. The change in intraocular pressure during this time is computed as an arithmetical average of pressure increments for successive half-minute intervals (Ave. $P_t - P_o$). The C-value is then derived from Grant's equation:

$$C = \frac{\Delta V}{T (\text{Ave. } P_t - P_o)}$$

d. Perfusion studies of enucleated human eyes have supported Grant's equation, although newer tables used in the formula have given C-values far higher than those generally accepted.¹⁸¹ Sources of error in tonography include the following physiological and technical parameters.

3. *Other ocular parameters that influence tonography.* The tonographic calculation assumes that only the rate of aqueous outflow changes in response to a change in intraocular pressure. However, there are many other ocular parameters that respond to a pressure change, all of which can influence the tonographic result.

a. *Aqueous production decreases with a rise in intraocular pressure,* primarily due to an alteration in ultrafiltration.^{182, 183} The subsequent intraocular pressure drop in response to reduced production of aqueous creates an impression of increased outflow and is called *pseudofacility*. This accounts for up to 20% of the total C-value.¹⁸² Tonography measures the total C-value, without distinguishing between true facility and pseudofacility.

b. *Resistance to aqueous outflow increases with an increase in the intraocular pressure,* the physiologic basis of which was previously discussed. The tonographic result is that the C-value of an eye decreases with increasing intraocular pressure.¹⁸⁴ This phenomenon relates to the conventional, or canalicular, route of aqueous outflow. The influence of extracanalicular outflow on the tonographic result is not fully understood.

c. *Episcleral venous pressure rises an average of 1.25 mmHg with the pressure elevation during tonography,*¹⁸⁵ which is usually corrected for in the formula by adding 1.25 to P_o .

d. *Ocular rigidity is an expression of the "stretchability" of the eye in response to an increase in intraocular pressure and probably represents several characteristics of the eye.* An average ocular rigidity of 0.0125 is used in calculating the tonographic C-value, although there is significant interpatient variation in this parameter, which leads to a potential source of error in tonography. For this reason it is useful to check the pressure by applanation tonometry before performing the tonography and to compare this with the P_o obtained with the indentation tonometer, as a means of identifying any major discrepancy in ocular rigidity.¹⁷²

e. The expulsion of uveal blood in response to elevated intraocular pressure probably influences tonography, although the actual effect is uncertain.¹⁸⁶

C. Technique

The details of performing tonography are available in several excellent textbooks.^{164, 172, 176} The purpose of the present discussion is to provide an overview of the technique.

1. Basic steps.

a. With the recorder running, the electronic tonometer is calibrated at scale readings of 0 and 7. The recording needle is then set at 0 for the subsequent readings.

b. The patient is in a supine position, fixing on a target overhead. After instilling a topical anesthetic on the cornea, the intraocular pressure is measured with two brief applications of the electronic tonometer.

c. The 4-minute pressure tracing is then made by gently applying the tonometer to the cornea and maintaining this position until a smooth tracing has been obtained for a full 4 minutes. A good tracing will have fine oscillations and a gentle downward slope. If the slope is steeper or irregular during the first few seconds, which is not uncommon, the study should be continued until a good 4-minute tracing has been obtained.

d. The slope of the tracing is then estimated by placing a free hand line through the middle of the oscillations. The scale readings are noted at the beginning and end of the 4-minute tracing.

e. P_0 is determined from the initial scale reading and a standard calibration table. P_0 and the change in scale readings over the four minutes (ΔR) are then used to obtain the C-value from special tonographic tables.

2. Sources of error.

a. Variations in corneal curvature from the assumed average of 7.8 mm may significantly influence the pressure measurements.¹⁷⁶

b. *Moses effect.* The hole in the tonometer footplate must be slightly larger in electronic tonometers to prevent sticking. At low scale readings, the cornea may mold into the space between the plunger and hole, pushing the plunger up and leading to falsely high pressure readings.¹⁸⁷

c. *Variations in line voltage* may produce an apparent drift in the intraocular pressure measurements, which can be minimized with line voltage stabilizers and by avoiding magnetic fields.¹⁷⁸

d. *Consensual pressure drop.* The intraocular pressure has been shown to drop approximately 1 mmHg in the fellow eye while tonography is being performed on the first eye. A neural etiology has once postulated for this phenomenon, but it was subsequently found to be secondary to the evaporation that results from keeping the eye open for fixation during the 4-minute test.¹⁸⁸ The problem can be eliminated by draping a plastic sheet over the fellow eye, while the first eye is being tested.¹⁸⁸

e. *Patient relaxation effect.* During the first 15 to 20 seconds after the tonometer is placed on the cornea, the IOP will fall as the patient relaxes. Time should be allowed for this before starting the 4-minute tracing. Other patient-related factors, such as blinking, squeezing, or lack of fixation during the test, can also lead to a poor tonographic result.

f. *Operator error,* including improper cleaning, calibration, or positioning of the instrument, as well as improper calculation of the tracing, can also lead to inaccurate results.

D. Interpreting Tonographic Results

Despite the many potentials for error in tonography and the possibility that currently accepted values may be grossly inaccurate, it is nevertheless necessary to be familiar with the values that might be anticipated with current techniques.

1. In a study of 1379 eyes, Becker¹⁸⁹ reported the following values:

a. C-value

- (1). The mean in 909 normal eyes was 0.28 $\mu\text{l}/\text{min}/\text{mmHg}$.
- (2). The prevalence of low C-values was:

C-Value	Normals (n = 909)	Glaucoma Patients (n = 250)	Family History of Glaucoma (n = 220)
<0.18	2.5%	65%	20%
<0.13	0.15%	43%	11%

b. Po/C ratio

- (1). The mean of the normal population was 56.
- (2). The prevalence of high Po/C ratios was:

Po/C Ratio	Normals	Glaucoma Patients	Family History of Glaucoma
>100	2.5%	73%	21%
>138	0.15%	50%	14%

2. In a study of 7,577 eyes, the C-value was found to decrease with age, with an average of 0.2932 for ages 41 to 45 years, compared to 0.2518 in the 81- to 85-year-old group. There was no sex difference at any age level.¹⁹⁰

3. When the C-value and Po do not seem to correlate, the following possibilities should be considered.¹⁷⁶

a. A low C with a normal Po may be due to:

- (1). a sticky tonometer
- (2). low ocular rigidity
- (3). hyposecretion

b. A high C with elevated Po may be due to:

- (1). an artificially elevated Po
- (2). high ocular rigidity
- (3). high pseudofacility
- (4). elevated episcleral venous pressure
- (5). angle-closure glaucoma (the force of the tonometer may open the angle)

- (6). the Moses effect
4. The wave components of a tonographic tracing include¹⁹¹:
 - a. Fine oscillations, which reflect the cardiac pulse.
 - b. Large waves, which reflect the respiratory movement.
 - c. Still larger, irregular waves (Traube-Hering waves), which reflect periodic oscillations in the systemic blood pressure.
 - d. Cardiac irregularities, e.g., extrasystoli, bigeminy, etc., can also cause irregularities in the tonographic tracing.

E. The Clinical Value of Tonography

As previously noted, there is controversy regarding the value of tonography in the detection and management of glaucoma. The following are the main situations in which tonography is felt by some physicians to have clinical value:

1. As an adjunct in diagnosing open-angle glaucoma, tonography is suggested to have predictive value regarding the development of nerve damage in patients with elevated intraocular pressure,¹⁹²⁻¹⁹⁴ though this has not been confirmed in all studies.¹⁹⁵ The Po/C ratio is generally felt to be the more sensitive parameter in this situation,¹⁹²⁻¹⁹⁴ and a prior water-drinking test (discussed in Section Two under Open-Angle Glaucoma) has been suggested to further enhance the predictive value of tonography.¹⁹² However, it has been stressed that abnormal tonometric and tonographic results do not make the diagnosis of glaucoma, but alert the ophthalmologist to follow the patient more closely.¹⁹⁶

2. A low C-value was felt to correlate with a wider diurnal fluctuation in intraocular pressure, but a study of 388 eyes showed that a single tonometric reading correlated with the diurnal curve better than did the tonographic results.¹⁹⁷

3. In angle-closure glaucoma, a 25 to 30% fall in the C-value may be used as adjunctive confirmation of a positive provocative test. In addition, once an acute attack is broken, a C-value of 0.10 or less suggests that a peripheral iridectomy alone may be insufficient.¹⁷⁶

4. Ocular inflammation, as with surgery, trauma, disease, etc., may mask a compromised outflow system by temporarily reducing aqueous production, and tonography during this time can disclose the abnormal outflow.¹⁷⁶

5. Additional suggested values for tonography include an adjunct in the diagnosis of myasthenia gravis by observing a rise in IOP of 2 to 5 mmHg in response to intravenous tensilon.¹⁹⁸

6. Since both aqueous and blood are expelled from the eye in variable amounts during tonography, it may be that a future value of tonography lies in its ability to assess the posterior half of the eye, portion directly related to visual loss, by measuring the blood-ejection coefficient.^{186, 199}

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